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Health-related Quality of Life of patients with malignant pleural mesothelioma treated with pemetrexed disodium

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In order to further describe the impact of pemetrexed disodium (ALIMTA®), health-related quality of life (HRQoL) assessment was included in a multinational phase II trial for patients with malignant pleural mesothelioma (MPM). Because no MPM-specific HRQoL instrument was available, a modified version of the Lung Cancer Symptom Scale (LCSS) form for patients was used. Separate data demonstrate that the modified LCSS is reliable and valid for MPM patients. Patients completed the LCSS two times before the start of therapy and then weekly while on-study. Patients with unresectable MPM who had not been previously treated with systemic chemotherapy received ALIMTA 500 mg/m2 every 3 weeks. LCSS data were averaged for baseline and for each cycle. Preliminary results from 62 patients were as follows: 87% male, median age=62 (range 40-80), median KPS=90 (range 70-100), 85% stage III-IV. Baseline median LCSS scores (scale 0-100, 0=best possible) were as follows: anorexia=20; fatigue=29; cough=8; dyspnea=35; hemoptysis=0; pain=22; symptom distress=27; activity level=44; and global QoL=26. Based on previously reported meaningful change of 10 points, using Cycle 3 data (after first on-study tumor assessment and 3 doses of ALIMTA), patients were grouped by best study response and categorized as improved, preserved or deteriorated for each LCSS item. Percentage of responding patients (N=9) with improved and preserved scores, respectively, were: anorexia (56%, 33%); fatigue (33%, 33%); cough (44%, 56%); dyspnea (33%, 67%); hemoptysis (0%, 100%); pain (33%, 44%); symptom distress (56%, 22%); activity level (56%, 33%); and global QoL (44%, 44%). Percentage of patients with stable disease (N=32) with improved and preserved scores, respectively, were: anorexia (16%, 37%); fatigue (23%, 35%); cough (22%, 53%); dyspnea (15%, 50%); hemoptysis (0%, 100%); pain (12%, 50%); symptom distress (13%, 35%); activity level (16%, 37%); and global QoL (6%, 50%). These preliminary LCSS results indicate that most patients receiving ALIMTA had stable or improved HRQoL during Cycle 3. Responders were more likely to report improvement, indicating that the modified LCSS is responsive to changes in clinical status.

Paediatric oncology

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Risk factors in malignant extracranial germ cell tumours (MGCTs) of childhood: Analysis of UKCCSG's GCII study

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Purpose: Most national groups now obtain high cure rates in paediatric extracranial MGCTs, mostly using cisplatin-based chemotherapy. In the UK carboplatin is preferred because it is less oto- and nephrotoxic. An analysis was performed to determine whether therapy should be based on risk factors.

Methods: Children aged 0–16 years with histologically verified extracranial MGCTs were excised if feasible without major morbidity, or biopsied. Chemotherapy with JEB (carboplatin, etoposide and bleomycin) was given if excision was incomplete or if tumour recurred after excision. Uni- and multivariate analyses of survival were performed.

Results: Between January 1989 and December 1997 192 patients were registered of whom 8 were excluded (no histology in 3, non-protocol chemotherapy in 5). The remaining 184 patients had germinoma (20), malignant teratoma (55), embryonal carcinoma (1), yolk sac tumour (107) or choriocarcinoma (1). Age, site and histology followed recognised patterns: yolk sac tumours in children aged <5 years; germinomas mostly in older children; malignant teratoma in all age groups; site of primary was also age related.

Univariate analysis of JEB treated patients showed 5 year EFS%

Testis	100	Stage I	100	Germinoma	100
Ovary	91	Stage II	94	Malignant teratoma	87
Vagina/uterus	80	Stage III	85	Yolk sac tumour	86
Sacrococcygeal	87	Stage IV	78		
Thorax	75			AFP < 10,000	95
Other	73			AFP ≥ 10,000	77

Surgery alone cured 47 patients and 137 required JEB. Overall 5 year survival was 93.2%. For JEB treated patients OS was 90.9% and EFS 87.8%

Multivariate analysis showed AFP level followed by stage and then site were the strongest risk factors and identified risk groups.

Conclusion: AFP level, stage, site and histology should be used to stratify patients for treatment.

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The prognostic value of histological subtype and tumor volume in localized unilateral nephroblastoma

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Today the prognosis of nephroblastoma is excellent. Questions arising in the management of children with nephroblastoma are mainly focusing on preventing late effects and in finding new prognostic risk factors.

Purpose: A retrospective analysis was performed to investigate the influence of histological subtypes and tumor volume on prognosis in nephroblastoma. Method: From April 1994 to December 2000 808 patients with a nephroblastoma were enrolled in the SIOP 93-01/GPOH study. 622 of them had stage I, II or III disease at diagnosis. In 352 of these patients tumor volume was measured by ultrasound at diagnosis and after preoperative chemotherapy. Histology was reviewed according to the Stockholm working classification.

Results: 10% had low risk, 78% intermediate risk and 12% high risk tumors. Relapse free survival after 5 years (RFS) for patients with localized unilateral nephroblastoma receiving preoperative chemotherapy is 93% for low risk, 91% for intermediate risk, and 79% for high risk tumors. Of the intermediate risk tumors epithelial and stromal predominant tumors show the best outcome with 98% RFS, compared to 81% for blastemal predominant tumors and 91% for all other subtypes of intermediate risk ($p<0.01$). In these patients a median tumor volume of 360 ml was measured at diagnosis and of 160 ml after preoperative chemotherapy. No tumor volume reduction was found in patients with low risk tumors (except completely necrotic tumors), in epithelial and stromal predominant tumors and in all high risk tumors (non-responsive tumors). In all other tumors (responsive tumors) a median tumor volume reduction of 180 ml did occur. The difference in tumor volume reduction between responsive and non-responsive tumors is highly significant ($p<0.01$). Patients with a localized unilateral nephroblastoma and a tumor volume of less than 500 ml after preoperative chemotherapy have a RFS of 89% compared to 72% for those with a larger tumor ($p<0.01$). By combining histological subtype and tumor volume after preoperative chemotherapy the intermediate risk tumors can be divided into 4 prognostic different subgroups: epithelial or stromal predominant (98% RFS), blastemal predominant (81% RFS), rest of intermediate risk and < 500 ml tumor volume (92% RFS), rest of intermediate risk and > 500 ml tumor volume (71% RFS).

Conclusion: Tumor volume after preoperative chemotherapy as well as the histological subtype can be used for further stratifying postoperative treatment.

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Synovial sarcoma in childhood and adolescence in the CWS 81-96 trials

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Objectives: To show event free and overall survival rates in Synovial Sarcoma (SySa) treated with a multimodal therapy concept. To define risk factors for future stratification for SySa, the third most common sarcoma in childhood and adolescence

Patients and Methods: We analyzed a group of 103 pts. enrolled in the CWS 81 to 96 studies (median age 13y, 0.1-20 years), minimum F/u of 30 months (for living pts.); median F/u 63 months (6-195). Postsurgical stage was IRS Group I in 34, II in 30, III in 30 and IV 9 pts. Sites: extremities 87 (21 upper, 62 lower limb), trunk 8, head/neck 8 pts.. 102 (99%) pts. received chemotherapy (VAIA, VACA, EVAIA or CEVAIE), 76 (74%) radiation therapy (16-60 Gy), 25 (24%) secondary surgery. Only 7

had non organ saving surgery (en bloc resection, amputation) in first line treatment.

Results: 5y EFS was 81%, 81%, 73% and 22%; 5 y SUR was 90%, 89%, 70% and 22% for IRS Group I, II, III and IV pts., respectively (p<0.001 for localized vs. metastatic). Univariate analysis revealed the following risk factors for localized disease: Tumor size <5cm vs >5cm (5y EFS 63% vs. 91%, p=0.001; 5y SUR 69% vs. 96%, p=0.002); histology biphasic vs. monophasic (5y EFS 89% vs 69% p<.03 5y SUR 90% vs 76%, n.s.). Radiotherapy no/yes (5y EFS 56% vs. 85%, 5y SUR 59% vs. 90%). Site: extremeties vs. trunk vs. head/neck (5y EFS 81% vs. 67%, vs. 60%, n.s.; 5y SUR 85% vs. 88%, vs. 67%, n.s.). No difference for T1/2 and age </>10y. No difference in 5y EFS and 5y SUR in IRS group I or II pts. between ifosfamide and cyclophosphamide containing regimen. Response to chemotherapy (week 9-12) was >2/3 tumor volume reduction in 13/27 (48%), >1/3 and <2/3 in 3/27 (11%) and non response in 11/27 (41%). Overall local control rate for IRS group I-III was 88%, systemic control rate 89%. Multivariate analysis will be presented.

Conclusions: To our knowledge these results are superior to other published data concerning systemic control rate and EFS for patients with localized disease emphasizing the indication for systemic chemotherapy in SySa. Tumor size and initial metastases have a high impact on prognosis.

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Results of the German multinational GPOH-HD 95 trial: analysis of risk factors in pediatric Hodgkin's disease after combination chemotherapy with and without radiation

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Purpose: The aim of the multicenter trial GPOH-HD 95 was to maintain the excellent treatment results of previous studies in pediatric Hodgkin's disease(HD), however to minimize the risk of potential late effects caused by radiation therapy(RT). Analysis of treatment failures should guide the planning of new protocols in the future.

Methods: Children below the age of 18 years were treated according to risk factors (stage,B-symptoms,extranodal extension) within 3 different treatment groups(TG) with 2,4 or 6 cycles of chemotherapy(CTx).When a complete remission could be achieved no consolidating RT followed.When a tumor reduction of >75% was obtained the RT-dose to involved fields(IF) was 20Gy,otherwise 30Gy, remaining lymphomas of >50ml were treated locally to 35Gy.Quality assessment of radiation therapy with review of radiaton protocols, planning and verification films was carried out centrally, as well as the analysis of treatment failures.

Results: From August 1995 to March 2001 a total of 956 eligible patients were registered from 126 institutions in European countries. At a median follow-up time of 34 months relapse free survival for the low risk group TG1(stage I/IIA) is 95%; for the intermediate risk(TG2) and advanced cases(TG 3) RFS is 94% and 92% with RT after chemotherapy induced PR and 79% after achieving a CR and no adjuvant RT, this difference is now statistically significant with a p-value of 0.006.However, overall survival is excellent with 97% for all pts., 99% for TG1 and 96% for TG3.- 71 events occurred, 65 of them were treatment failures (29 progressive disease during CTx, before,during or shortly after RT and 36 relapses). Risk factors for early failures were advanced stages, extranodal extension of disease, B-symptoms and nodular sclerosis type 2 histology.Risk factors for relapses were different for irradiated and not irradiated pts.Of importance seems to be the time lag between end of CTx and start of RT. Minor protocol violations in RT techniques did not show a major impact on treatment failures.

Conclusion: The omission of RT after achieving a CR with CTx causes an increased risk of treatment failures in advanced cases, however the total incidence of failures is low and has no impact on survival. The potential gain by reducing radiation dose and volume with respect to treatment induced long term toxicity might be considerable for the young patient population.

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Randomised trial comparing high-dose-methotrexate plus doxorubicine versus high-dose-methotrexate plus etoposide-ifosfamide as preoperative treatment for osteosarcomas

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Intensive high-dose-Methotrexate containing regimens (ie T10 protocol) produce the best results in term of EFS for the treatment of osteosarcomas. In the original T10, high-dose-Methotrexate was associated with Bleomycin-Cytoxan-Dactinomycin and Doxorubicin during the preoperative phase. Recently we have reported a 50% response rate with the combination of Etoposide-Ifosfamide in relapsing osteosarcoma patients.

Objectives: To improve the efficacy of the preoperative chemotherapy in osteosarcomas we have conducted a randomized trial comparing high-dose-Methotrexate 12gr/m2 (7 courses) associated with Doxorubicin 70 mg/m2 (2 courses) or with Etoposide 75 mg/m2/day-Ifosfamide 3 gr/m2/day x 4 days. The main criteria was the percentage of good histological responses (<5% viable cells). To provide an 80% power to detect a 20% difference in good responder rates between the 2 groups, for an overall level 2a = 5%, requires 226 pts.

Methods: 227 non metastatic, limb, osteosarcoma patients, aged 3 to 19 years, have been randomized (Doxorubicin 113, Etoposide-Ifosfamide 114). Surgery was conservative in 214 patients and radical in 13.

Results: 47 pts had a good histological response in the Doxorubicin arm (42%) and 61 pts in the Etoposide-Ifosfamide arm (54%) (information missing in one patient). The observed difference between the percentage of good responders between the 2 arms is 12% (p=0.06, CI 95% -0.5% +25%). For the whole population, the EFS3y is 70%.

Conclusions: The12% difference in favor of Etoposide-Ifosfamide does not reach statistical significance. Taking into account the potential long term toxicity, Etoposide-Ifosfamide appears less toxic than Doxorubicin and will be considered as a better arm in future studies.

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Children nasopharyngeal carcinoma

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Purpose: To report the epidemiological, clinical and therapeutic features of pediatric Nasopharyngeal carcinoma among Tunisian children.

Materials and Methods: Our retrospective study concerned patients aged less than 16 years affected by histological proven Nasopharyngeal carcinoma. Initial work-up included: clinical examination with measures (cervical nodes square), chest-x ray, abdominal ultrasonography, bone scintigraphy. We used the UICC-AJC 1987 classification.

Results: We collected 34 patients (20 M/14 F) from 1980 to 1998, with a mean age of 13.7 years (10 to 16) and a 1.4 sex-ratio. Mean delay to consultation is 5.8 months (1 to 51) and symptoms dominated by cervical nodes (91%) or more rarely rhino logic (56%), neurological signs (38%) of otologic signs (29%). Paraneoplastic syndromes were seen in 9 cases (26%). Tumors are mainly posterior (61%) and fun gating (62%). Nodes are predominantly in the high and posterior cervical area with a mean diameter of 4.8 cm (1 to 10) and mean surface of 22.5 cm2 (2 to 80). 74% of patient presented with T3–4 tumors and 82% with N2–3 nodes. Undifferentiated histological type predominate representing 94.2% of cases. All patients received loco - regional radiotherapy while 27 received chemotherapies mainly neoadjuvant and cisplatin based. With a median follow-up of 58 months (10 to 168), 5-years survival and disease-free survival are 58% and 55% while loco-regional control rate is 90%. Failures were dominated by metastases observed in 10 patients (37%) mainly in bones and loco-regional relapses ate observed in 2 patients (7.5%). Multifactor analysis showed a prognostic value for loco-regional control of delay to consultation (p = 0.001), nodal surface > 20 cm2 (p = 0.04) and cranial nerve palsies (p = 0.02), for overall survival the importance of delay to consultation (p = 0.05), sex (p = 0.03), neoadjuvant chemotherapy (p = 0.03) and cervical nodes surface (p = 0.05), for metastasis-free survival the impact of delay to diagnosis (p = 0.05) and nodal surface (p = 0.05) and for disease-free survival the impact of delay to consultation (p = 0.04).

Conclusion: The child's nasopharyngeal carcinoma is relatively frequent in Tunisia. The clinical presentation is often comparable adult nasopharyn-